REMARKS

Claims 2-7 are pending in the present application and are rejected. Applicants' representative thanks the Examiner for the courtesies extended in the telephone interview of June 28, 2007. Applicants' statement of the substance of the interview is incorporated herein.

Applicant's Response to Claim Rejections under 35 U.S.C. §103

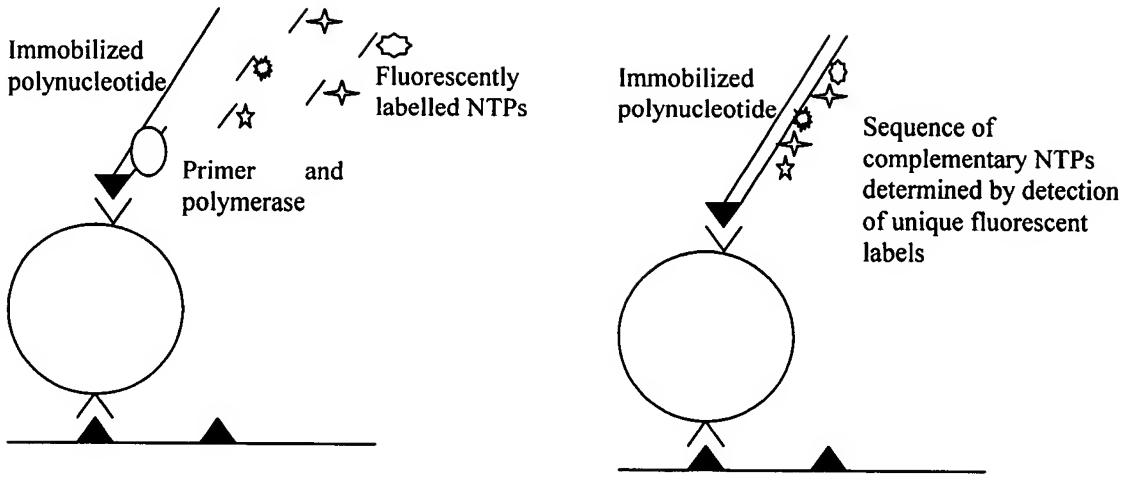
Claims 2, 4, 5 and 7 were rejected under 35 U.S.C. §103(a) as being unpatentable over Balasubramanian et al. (WO 00/06770) in view of Bruchez et al. (U.S. Patent Application No. 2001/0034034).

It is the position of the Office Action that Balasubramanian discloses the invention as claimed, with the exception of teaching spatially addressing the beads by an antigen-antibody reaction. The Office Action relies on Bruchez to provide this teaching.

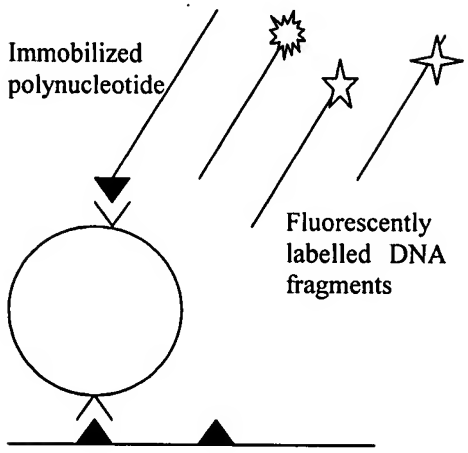
Balasubramanian is directed at arrayed biomolecules and their use in sequencing. As illustrated in Figure 2, Balasubramanian contemplates an array in which a microsphere 1 is bound to a substrate by an association between streptavidin 2 formed on the microsphere 1 and biotin 3 formed on the substrate. Additionally, a fluorescently labeled polynucleotide 4 is attached to the microsphere bead 1 by an association between streptavidin 2 formed on the microsphere and biotin 3 bound to the end of the polynucleotide. It is the position of the Office Action that this construction is similar to that illustrated in the Request for Reconsideration filed on February 27, 2007.

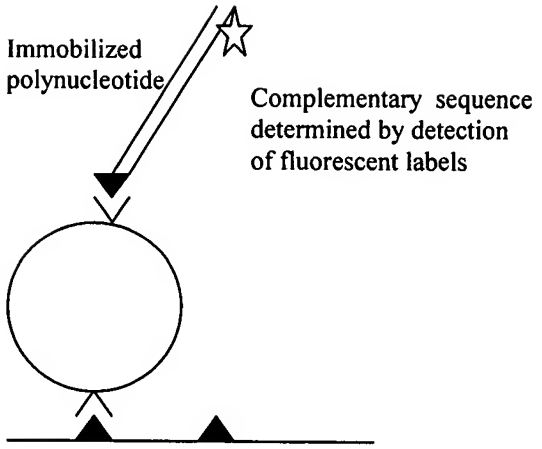
The preparation of the array illustrated in Figure 2 is discussed in detail in Example 1 from page 14, lines 7 to page 15, line 28. First, biotin is deposited on the glass substrate. Page 14, lines 30-32. Next, non-fluorescent streptavidin functionalized polystyrene latex microspheres are deposited on the substrate. Microspheres are bound by a streptavidin/biotin reaction and non-bound microspheres washed off. Page 15, lines 1-6. Next, biotinylated single-stranded-DNA is bound to the microspheres by a streptavidin/biotin reaction, and excess single-stranded-DNA is washed off. Page 15, lines 12-15. Balasubramanian contemplates situations in which the molecules in the array are all the same, and situations in which many different molecules are arrayed. Page 5, lines 20-24. Once formed, "[t]he arrays may be used in many different analysis procedures or characterization studies." Page 3, lines 19-21.

One preferred sequencing method is described at page 3, lines 22-32. Briefly, a single stranded polynucleotide is fixed immobilized on the array (for example, via a microsphere, as discussed above). Then, using a primer, polymerase, and different NTPs each bound with a different fluorescent label, the sequence of the immobilized polynucleotide may be determined. Each NTP added, and the corresponding fluorescent label, may be detected. Thus, the polynucleotide complementary to the immobilized polynucleotide may be determined. This method is represented by the illustration below:



Another method is described at page 4, lines 6-12. Target molecules may be brought into contact with and bound to the immobilized polynucleotides, which are of a predetermined sequence. The target molecules are labeled with a fluorescent label, thus, it can be detected whether a hybridization has occurred. Balasubramanian also identifies a method in which the array of immobilized polynucleotide is contacted with a plurality of labeled fragments of DNA, and hybridization events detected. See page 4, lines 13-18. These two methods appear to be very similar and are represented by the illustration below.





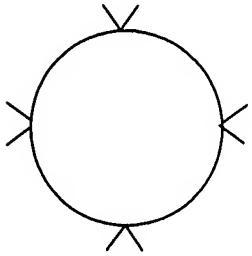
With regard to "addressing" the array, this is not through an interaction between the microsphere 1 and the substrate. Attachment of the beads is via a streptavidin/biotin reaction. This reaction is non-specific in that all microspheres are only labeled with streptavidin, and the entire substrate is only labeled with biotin. Additionally, all polynucleotides are only labeled with biotin. Thus, there is no specificity in the manner in which the microsphere attaches to the substrate or in which the polynucleotide attaches to the microsphere. Instead, "addressing" is conducted by detection of the above-referenced fluorescent tags, for example. See page 10, line 22 to page 11, line 24.

In the telephone interview of June 28, 2007, the Examiner stated that she disagreed with Applicants' representative regarding the disclosure of Balasubramanian. Applicants' representative posited that Balasubramanian only discloses hybridizing the target biomolecule with the probe biomolecule after the microsphere is immobilized on the substrate. Thus, Applicants' representative argued that Balasubramanian does not disclose "hybridizing in

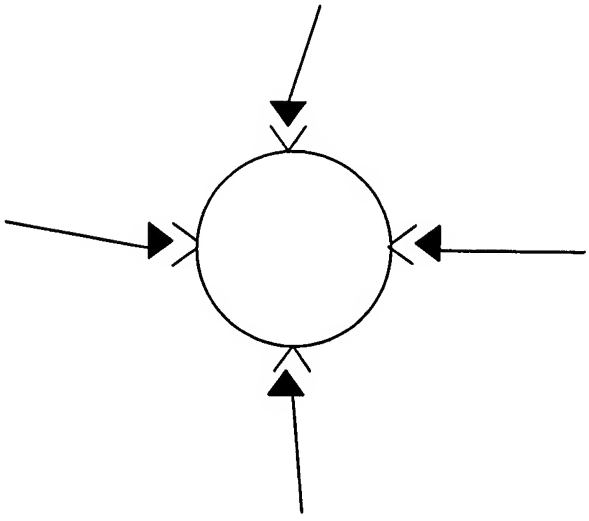
solution." On the other hand, the Examiner was of the position that Balasubramanian additionally discloses hybridizing the target biomolecule with the probe biomolecule before attaching the microsphere to the substrate. Accordingly, the Examiner argued that Balasubramanian discloses "hybridizing in solution."

In response, Applicants respectfully submit that Balasubramanian never disclose "hybridizing in solution." Rather, the Office Action relies on a broad interpretation of isolated vague passages of Balasubramanian. As evidence of the fact that Balasubramanian does not disclose "hybridizing in solution" before immobilizing the microsphere on the substrate, Applicants respectfully submit that such an embodiment of Balasubramanian would not function properly. Although Balasubramanian only identifies the above method of attaching the microsphere to the substrate prior to hybridizing in Example 1, the Office Action that Balasubramanian also discloses, but does not provide an example of, an alternate method in which the hybridization would occur prior to attaching the microsphere on the substrate. Although Applicants reiterate that such a method is not disclosed by Balasubramanian, it appears that the theorized method would be as illustrated in the following crude exemplary drawings and the corresponding comments:

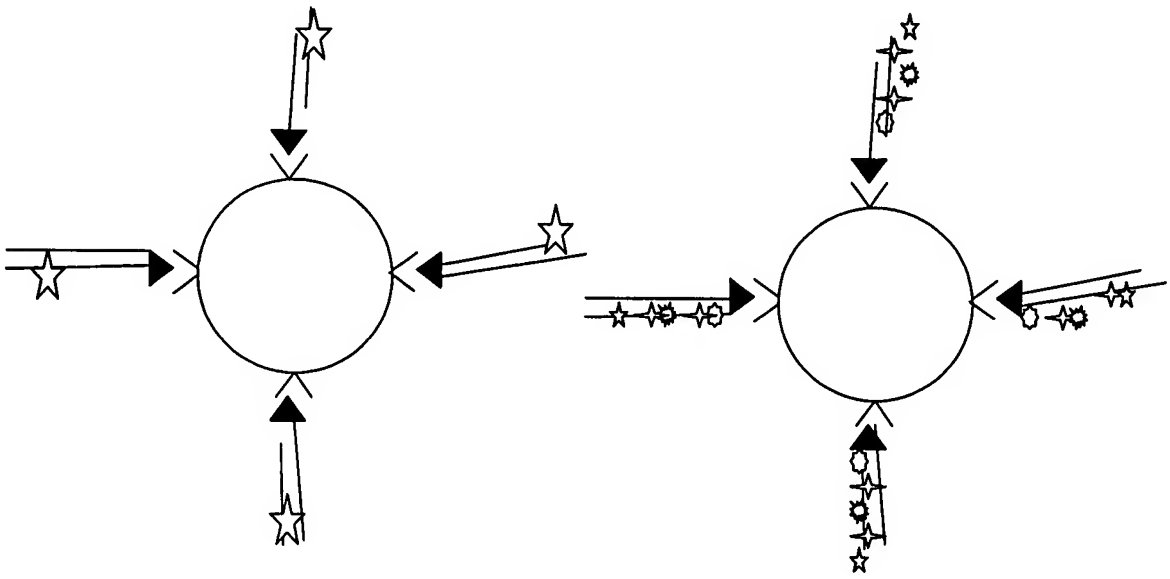
First, a microsphere would be coated with non-fluorescent streptavidin (for simplicity, only four streptavidin sites are illustrated):



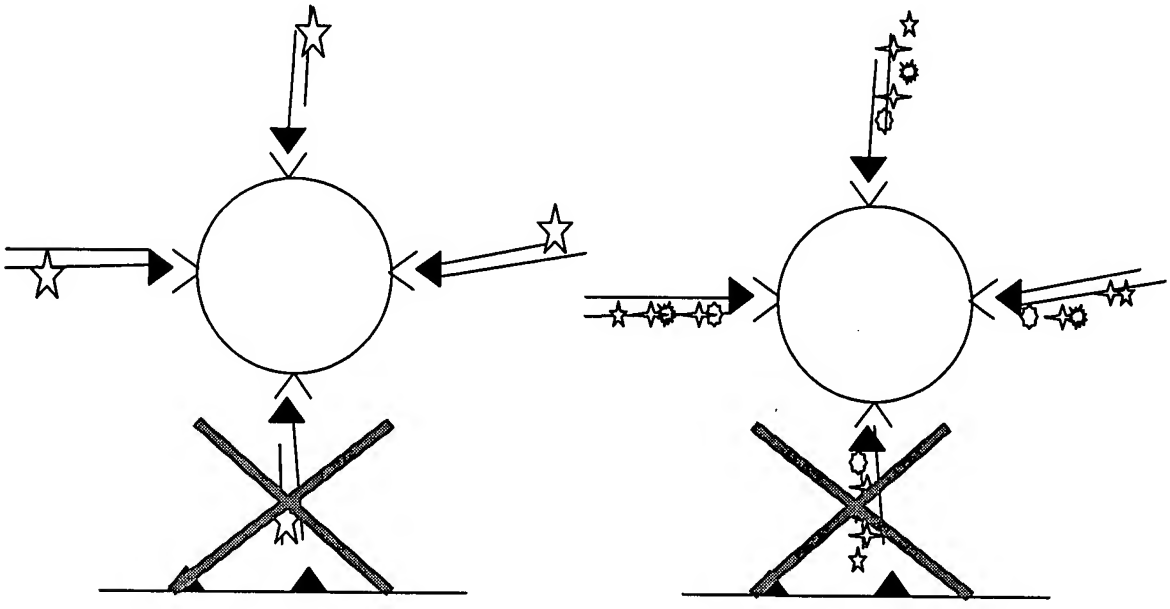
Next, biotinylated single-stranded-DNA would be bound to the microspheres by a streptavidin/biotin reaction:



Then, the single-stranded-DNA would either be (1) hybridized with a target biomolecule labeled with a fluorescent tag, or (2) reacted with a polymerase and fluorescently-labelled NTPs. The results would be as illustrated below:



Finally, the combination of the microsphere, probe and target would be coupled to the substrate via biotin/streptavidin binding.



However, the microspheres would be unable to attach to the substrate, because all of the streptavidin sites on the microsphere would be bound to the biotinylated single-stranded DNA, which in turn was hybridized to either a target biomolecule or a synthesized biomolecule. Accordingly, it is clear that the alternative embodiment posited by the Examiner in the telephone interview would not work. Thus, it is clarified that this embodiment is not disclosed by Balasubramanian. Being that biotin and streptavidin have a very high affinity for each other, the biotinylated single-stranded DNA would clearly bind to every streptavidin site. Even if there was a remaining streptavidin site, the microsphere would be unable to bind to substrate, due to the steric interference of the single-stranded DNA and the hybridized target biomolecule or the synthesized biomolecule.

In the interview, the Examiner relied upon isolated passages of Balasubramanian to support the position that the reference also discloses "hybridizing in solution." For instance, the Examiner identified the passage at page 4, lines 19-20, which states that "[a]n array of the invention may be used to generate a spatially addressable array of single polynucleotide molecules," and the passage at page 10, lines 16-18, which states that "[i]n this context, term "spatially addressable" is used to describe how different molecules may be identified on the basis of their position in the array."

However, Applicants respectfully submit that upon further review of the reference, these statements are consistent with the disclosed and described method of hybridizing <u>after</u> attachment of the bead to the substrate. As discussed above, after immobilizing the microsphere having an attached single stranded DNA to the surface, either (1) a fluorescently-labelled target

biomolecule will hybridize to the single stranded DNA, or (2) a biomolecule complementary to the single-stranded DNA will be synthesized using fluorescently-labelled NTPs and a polymerase. Subsequently, these target biomolecule or the synthesized biomolecule will be sequenced using known non-destructive techniques. Thus, the sequence and location of the target biomolecule or synthesized biomolecule can be known. Accordingly, the sequence and location of the corresponding single-stranded DNA can be known. Then array can then reused for high throughput sequencing. See page 10, line 14 to page 11, line 21. Thus, the procedure of Balasubramanian is a crude solution to the problem identified in the specification ate page 3, line 4-6. In other words, the bead-based method of Balasubramanian is unsatisfactory in that the DNA attached to the bead is initially unknown. In order to resolve the sequence of the DNA, Balasubramanian requires nondescructive sequencing of a complementary sequence, before the position of each DNA of the array may be known. This is expensive and time consuming.

Therefore, Applicants respectfully submit that Balasubramanian does not disclose or suggest an embodiment including "hybridizing in solution" a target and a probe. The entire disclosure of Balasubramanian is only consistent with an embodiment in which the target and probe are hybridized after the immobilization of the microsphere on the substrate. Although selected vague passages of Balasubramanian are interpreted by Office Action to disclose "hybridizing in solution," it is improper to identify these passages as the teachings of Balasubramanian. It is impermissible...to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full

appreciation of what such reference fairly suggests to one skilled in the art. *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965).

Next, Applicants discuss the disclosure of Bruchez. Bruchez is directed at a method of detecting an analyte in a sample using semiconductor nanocrystals as a detectable label. Bruchez discloses several different ways for a nanocrystal or "Qdot" to be attached. In the embodiment illustrated in Figure 1A and discussed in Example 1, a primary antibody is attached to a substrate. A sample including an analyte of interest is then added and binds to the primary antibody. A secondary antibody attached to a Qdot then binds to the analyte of interest. The fluorescence of the bound Qdots is then determined. Thus, the presence of a desired analyte in the sample can be determined.

In the embodiment illustrated in Figure 1B and discussed in Example 2, a sample containing an analyte of interest is adsorbed onto a substrate. An antibody attached to a Qdot is then bound to the analyte of interest adsorbed onto the substrate. The fluorescence of the bound Qdots is then determined. Thus, the presence of a desired analyte in the sample can be determined.

In the embodiment illustrated in Figure 1C and discussed in Example 3, Qdots are bound to microspheres via an antibody-analyte structure or an antibody-analyte-antibody structure. However, these microspheres are never bound to a substrate. Rather, detection is done by flow cytometry. Thus, the embodiment illustrated in Figure 1C is not germane to the present invention or the disclosure of Balasubramanian, since these are related to arrays.

In response to the rejection, Applicants respectfully submit that the combination of references does not disclose or suggest the invention as claimed. In particular, the combination of Balasubramanian and Bruchez does not disclose or suggest "hybridizing in solution" said target biopolymers and said probe biopolymers fixed to said beads. In the present invention, the target RNA/DNA 4 are hybridized in solution with the probe DNA 2, while the probe DNA is fixed to beads 1. This is illustrated in Figures 1 and 3 of the application. In other words, the probe DNA is already bound to the bead when it is hybridized with the target RNA/DNA.

As discussed above, Balasubramanian only discloses hybridizing the probe and target after the microspheres have been immobilized on the substrate. Thus, the combination of the cited references would result in an array which is formed by depositing an antibody on a substrate, attaching a corresponding antigen to a microsphere, binding the microsphere to the substrate by the antibody-antigen reaction, and then attaching a single-stranded DNA to the microsphere by the antibody-antigen reaction. Finally, the probe would be hybridized with a target. However, such a combination would not disclose "hybridizing in solution" a probe DNA fixed to a bead with target RNA/DNA, as required by claim 7.

However, even if Balasubramanian were erroneously interpreted to disclose hybridizing the probe and target prior to immobilization of the microsphere, the combination of references would not disclose or suggest the invention as claimed. Such a combination would result in an array which is formed by first attaching an antigen to a microsphere and then attaching an antibody-labeled single-stranded DNA to the microsphere by the antibody-antigen reaction. The microsphere having the single-stranded DNA attached via the antibody-antigen reaction would

then hybridize with a target. Next the antibody would be deposited on a substrate. However, such a combination would not include "capturing said beads-ID recognizting address linkers fixed to said bead by an antigen-antibody reaction." As similarly discussed with respect to Balasubramanian above, all antigen sites on the bead would be occupied by the antibody-labelled single-stranded DNA. Furthermore, steric interferences would prevent the microsphere from attaching to the substrate.

Therefore, for at least the above reasons, Applicants respectfully submit that the combination of references does not disclose or suggest the invention as claimed. Favorable reconsideration is respectfully requested.

Claim 3 was rejected under 35 U.S.C. §103(a) as being unpatentable over Balasubramanian in view of Bruchez and further in view of Collier (U.S. Patent No. 5,985,548).

It is the position of the Office Action that the combination of Balasubramanian and Bruchez discloses the invention as claimed, with the exception of stirring beads. The Office Action relies on Collier to provide this teaching.

In response, Applicants respectfully submit that Collier does not make up for the teachings that Balasubramanian and Bruchez lack, as discussed above. Accordingly, Applicants respectfully submit that claim 3 is patentable at least due to its dependency on claim 7, which Applicants submit is patentable for at least the reasons discussed above.

Additionally, Applicants respectfully submit that one having ordinary skill in the art would not have been motivated to combine the teachings of Collier with that of Balasubramanian and Bruchez. The recitation of "said target biopolymers and said beads are put in a reservoir with a buffer solution and are stirred using a physical, electrical or chemical means" is simply a further limitation on the "hybridizing" step of claim 7.

As discussed above, the combination of Balasubramanian and Bruchez teaches that the microsphere is already attached to the substrate when the probe polynucleotide is added. Of course, the microsphere is also attached to the substrate when the target polynucleotide is added or generated by polymerization. Additionally, it appears that the Example 2 of Collier cited by the Office Action is illustrated in Figure 3. In such a method, the disclosed "agitation" would be conducted while the bead is attached to the substrate, as illustrated in steps (b)-(e) of Figure 3. Thus, although it may be obvious to combine the teachings of Collier with the embodiment of Balasubramanian which is clearly disclosed in Example 1, it would not have been obvious to combine the teachings of Collier with a method including a "hybridizing in solution." Therefore, for at least the above reasons, one having ordinary skill in the art would not have been motivated to combine the references. Applicants respectfully traverse the rejection. Favorable reconsideration is respectfully requested.

For at least the foregoing reasons, the claimed invention distinguishes over the cited art and defines patentable subject matter. Favorable reconsideration is earnestly solicited.

Should the Examiner deem that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

WESTERMAN, HATTORI, DANIELS & ADRIAN, LLP

Ryan B. Chirnomas
Attorney for Applicants
Registration No. 56,527
Telephone: (202) 822-1100
Facsimile: (202) 822-1111

RBC/nrp